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Philip C. Comp

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For:

BLOCKADE OF PROTEIN C ACTIVATION REDUCES
MICROVASCULAR SURGICAL BLOOD LOSS

Assistant Commissioner
for Patents
Washington, D.C. 20231

SEP 13 1995

GROUP 1800

INFORMATION DISCLOSURE STATEMENT

Sir:

The following publications, copies of which are enclosed, are cited in compliance with the duty of disclosure under 37 C.F.R. §1.56. Also enclosed is a check in the amount of \$210.00, the fee for consideration of this Information Disclosure Statement.

U.S. Patents

<u>U.S. Patents</u>	<u>Issue Date</u>	<u>Inventor</u>
5,084,273	01/28/92	Hirahara
5,093,117	03/03/92	Lawrence, et al.

Foreign Patent Applications

<u>Number</u>	<u>Publication Date</u>	<u>Country</u>
WO 94/22470	10/13/94	PCT

Publications

Bauer, K.A. and R.D. Rosenberg
290 SB 09/07/95 09743060
1126 Congenital
antithrombin III deficiency: insights into the pathogenesis of
210.00 CK

U.S.S.N. 08/323,060
Filed: October 14, 1994
INFORMATION DISCLOSURE STATEMENT

the hypercoagulable state and its management using markers of hemostatic system activation," *Am.J.Med.* **87**:39S-43S (1989)

Bauer, K.A. and R.D. Rosenberg, "Role of antithrombin III as a regulator of in vivo coagulation," *Semin.Hematol.* **28**:10-18 (1991)

Broze, G.J., Jr., et al., "The lipoprotein-associated coagulation inhibitor," *Prog.Hemost.Thromb.* **10**:243-268 (1991)

Broze, G.J., Jr., et al., "Regulation of coagulation by a multivalent Kunitz-type inhibitor," *Biochemistry*. **29**:7539-7546 (1990)

Chesebro, James H., et al., "Antithrombotic Therapy and Progression of Coronary Artery Disease," *Circulation Supplement III*, **86**(6):III-100-!!!-110 (1992)

Clouse, L.H. and Comp, P.C., "The regulation of hemostasis: The protein C system," *N. Engl. J. Med.* **314**(20):1298 (1986)

Comp, P.C. and Esmon, C.T., "Generation of fibrinolytic activity by infusion of activated protein C into dogs," *J. Clin. Invest.* **68**:1221 (1981)

Comp, P.C., et al., "Familial protein S deficiency is associated with recurrent thrombosis," *J. Clin. Invest.* **74**:2082-2088 (1984)

Comp, P.C., et al., "Activation of protein C in vivo," *J.Clin.Invest.* **70**: 127-134 (1987)

Comp, P.C., "Hereditary disorders predisposing to thrombosis," In B.S. Coller (Ed.), *Progress in Hemostasis and Thrombosis*. (New York: Grune and Stratton, 1986). Vol. 8, pp. 71-102

Conway, E.M. and R.D. Rosenberg, "Tumor necrosis factor suppresses transcription of the thrombomodulin gene in endothelial cells," *Mol.Cell.Biol.* **8**:5588-5592 (1988)

U.S.S.N. 08/323,060
Filed: October 14, 1994
INFORMATION DISCLOSURE STATEMENT

Cooper, D.K.C., et al., "The Pig as Potential Organ Donor for Man," Chapter 30, 481-500

Dahlback, B., "Interaction between vitamin K-dependent protein S and the complement protein, C4b-binding protein. A link between coagulation and the complement system," *Semin.Thromb.Hemost.* **10**:139-148 (1984)

Dahlback, B., "Inhibition of protein C cofactor function of human and bovine protein S by C4b-binding protein," *J.Biol.Chem.* **261**:12022-12027 (1986)

Dahlback, B., "Interaction between complement component C4b-binding protein and the vitamin K-dependent protein S. A link between blood coagulation and the complement system," *Scand.J.Clin.Lab.Invest. [Suppl]* **177**:33-41 (1985)

de Fouw, N.J., et al., "The cofactor role of protein S in the acceleration of whole blood clot lysis by activated protein C in vitro," *Blood* **67**:1189-1192 (1986)

Esmon, C.T., et al., "Interaction of thrombin with thrombomodulin," *Ann. N.Y. Acad. Sci.* **485**: 215 (1986)

Esmon, C.T., "The roles of protein C and thrombomodulin in the regulation of blood coagulation," *J. Biol. Chem.* **264**(9): 4743 (1989)

Esmon, N.L., "Thrombomodulin," *Semin.Thromb.Hemost.* **13**:454-463 (1987)

Flaherty, M.J., et al. "Iatrogenic immunization with bovine thrombin: A mechanism for prolonged thrombin times after surgery," *Ann. Int. Med.* **111**: 631 (1989)

Flaherty, M.J. and Wener, M.H., "Antibodies to thrombin in postsurgical patients," *Blood* **73**(5):1386 (1989)

Fulcher, C.A., et al., "Proteolytic inactivation of human factor VIII procoagulant protein by activated human protein C and its analogy with V," *Blood* **63**:486-49 (1984)

U.S.S.N. 08/323,060
Filed: October 14, 1994
INFORMATION DISCLOSURE STATEMENT

Hillarp, A. and B. Dahlback, "The protein S-binding site localized to the central core of C4b-binding protein," *J.Biol.Chem.* **262**:11300-11307 (1987)

Kirkman, Robert L., "Of swine and men: organ physiology in different species," *Xenograft 25* Mark A. Hardy (Ed.), 1989 Elsevier Science Publishers (Biomedical Division)

Kisiel, W., et al., "Anti-coagulant properties of bovine plasma protein C following activation by thrombin," *Biochemistry* **16**: 5824 (1977)

Kisiel, W., "Human plasma protein C: Isolation, characterization and mechanism of activation by alpha-thrombin," *J. Clin. Invest.* **64**: 761 (1979)

Lentz, S.R., et al., "Regulation of thrombomodulin by tumor necrosis factor-alpha: comparison of transcriptional and post-transcriptional mechanism," *Blood* **77**:542-550 (1991)

Marlar, R.A., et al., "Human protein C: inactivation of factors V and VIII in the activated molecule," *Ann.NY.Acad.Sci.* **370**:303-10 (1981)

Melissari and Kakkar, "Congenital severe protein C deficiency in adults," *Br. J. Haematol.* **72**(2):222-228 (1989)

Menache, D., "Antithrombin III: introduction," *Semin.Hematol.* **28**:1-2 (1991)

Miletich, J.P., "Laboratory diagnosis of protein C deficiency," *Semin. Thromb. Hemost.* **16**(2):169 (1990)

Miletich, J., et al., "Absence of thrombosis in subjects with heterozygous protein C deficiency," *N. Engl. J. Med.* **317**(16):991 (1987)

Moore, K., et al., "Endotoxin enhances tissue factor and suppresses thrombomodulin expression of human vascular endothelium in vitro," *J.Clin.Invest.* **79**:124-130 (1987)

Moore, K.L., et al., "Tumor necrosis factor leads to the internalization and degradation of thrombomodulin from the

U.S.S.N. 08/323,060
Filed: October 14, 1994
INFORMATION DISCLOSURE STATEMENT

surface of bovine aortic endothelial cells in culture
Indianapolis," *Blood* **73**:159-165 (1989)

Muller, James E., "Coronary Artery Thrombosis:
Historical Aspects," *J. Am. Coll. Cardiol.* **1**(3):893-896 (1983)

Nawroth, P.P., et al., "Interleukin 1 induces
endothelial cell procoagulant while suppressing cell-surface
anticoagulant activity," *Proc.Natl.Acad.Sci.USA* **83**:3460-344
(1986)

Nawroth, P.P. and D.M. Stern, "Modulation of
endothelial cell hemostatic properties by tumor necrosis factor,"
J.Exp.med. **163**:740-745 (1986)

Owen, W.G. and Esmon, C.T., "Functional properties of
an endothelial cell cofactor for thrombin-catalyzed activation of
protein C," *J. Biol. Chem.* **256**:5532 (1981)

Preissner, K.T., "Biological relevance of the protein C
system and laboratories diagnosis of protein C and protein S
deficiencies," *Clin. Sci.* **78**: 351, 1990

Rapaport, S.I., "Inhibition of factor VIIa/tissue
factor-induced blood coagulation: with particular emphasis upon a
factor Xa-dependent inhibitory mechanism 92013," *Blood* **73**:359-365
(1989)

Rapaport, S.I., "The extrinsic pathway inhibitor: a
regulator of tissue factor-dependent blood coagulation,"
Thromb.Haemost. **66** (1):6-15 (1991)

Snow, T.R., et al., "Protein C activation following
coronary artery occlusion in the in situ porcine heart,"
Circulation **84**:(1): 293 (1991)

Stearns, D.J., et al., "The interaction of a Ca^{2+} -
dependent monoclonal antibody with the protein C activation
peptide region. Evidence for obligatory Ca^{2+} binding to both
antigen and antibody," *J. Biol. Chem.* **263**: 826-832 (1988)

Stricker, R.B., et al., "Development of antithrombin antibodies following surgery in patients with prosthetic cardiac valves," *Blood* **72**(4):1375 (1988)

Taylor, F.B., et al., "Protein C prevents the coagulopathic and lethal effects of *Escherichia coli* infusion in the baboon," *J. Clin. Invest.* **79**: 918 (1987)

Trippodi, A., et al., "Asymptomatic homozygous protein C deficiency," *Acta Haematol.* **83**: 152 (1990)

Tuddenham, E.G., et al., "Homozygous protein C deficiency with delayed onset of symptoms at 7 to 10 months," *Thromb. Res.* **53**: 475 (1989)

Walker, F.J., "Protein C deficiency in liver disease," *Ann. Clin. Lab. Sci.* **20**(2):106 (1990)

Walker, F.J., Scandella, D. and Fay P.J., "Identification of the binding site for activated protein C on the light chain of factors V and VIII," *J. Biol. Chem.* **265**(3):1484-89 (1990)

Walker, F.J., "Regulation of activated protein C by protein S. The role of phospholipid in factor Va inactivation," *J. Biol. Chem.* **256**:11128-11131 (1981)

Walker, F.J., "Protein S and the regulation of activated protein C," *Semin. Thromb. Hemost.* **10**:131-138 (1984)

Walker, F.J., "Interactions of protein S with membranes," *Semin. Thromb. Hemost.* **14**:216-221 (1988)

Walker, F.J., et al., "Inactivation of factor VIII by activated protein C and protein S," *Arch. Biochem. Biophys.* **252**:322-328 (1987)

Walker, F.J., "Regulation of activated protein C by a new protein. A possible function for bovine protein S," *J. Biol. Chem.* **255**:5521-5524 (1980)

U.S.S.N. 08/323,060
Filed: October 14, 1994
INFORMATION DISCLOSURE STATEMENT

Remarks

This statement should not be interpreted as a representation that an exhaustive search has been conducted or that no better art exists. Applicant invites the Examiner to independently evaluate the cited art to determine its relevance to the subject matter of the present application.

Respectfully submitted,



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Dated: August 25, 1995

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CERTIFICATE OF MAILING (37 CFR 1.8a)

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Date: August 25, 1995



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